

03-26-01

JC14 Rec'd PCT/PTO
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J1057 U.S. PTO

FORM PTO-1390
(REV. 11-2000)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER

12964.23

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

09/806080

INTERNATIONAL APPLICATION NO.

PCT/EP99/07055

INTERNATIONAL FILING DATE

22 September 1999

PRIORITY DATE CLAIMED

22 September 1998

TITLE OF INVENTION

GENES OF THE 1-DEOXY D-XYLULOSE BIOSYNTHESIS PATHWAY

APPLICANT(S) FOR DO/EO/US JOMAA, Hassan

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. ☐ is attached hereto (required only if not communicated by the International Bureau).
 - b. ☒ has been communicated by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
 - a. ☒ is attached hereto.
 - b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
 - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
 - b. ☐ have been communicated by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). unsigned
10. ☒ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☒ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☒ Other items or information: Express Mail Certificate
Post card

PCT09

RAW SEQUENCE LISTING

DATE: 04/16/2001

PATENT APPLICATION: US/09/806,080

TIME: 10:33:02

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 C--> 10 <141> CURRENT FILING DATE: 2001-03-22
 12 <150> PRIOR APPLICATION NUMBER: DE19923567.8
 13 <151> PRIOR FILING DATE: 1999-05-22
 15 <150> PRIOR APPLICATION NUMBER: DE19843279.8
 16 <151> PRIOR FILING DATE: 1998-09-22
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 46 20 25 30
 48 aga aaa aat aac gca tat ata aat tat ggt ata gga tat aat gga cca 144
 49 Arg Lys Asn Asn Ala Tyr Ile Asn Tyr Gly Ile Gly Tyr Asn Gly Pro
 50 35 40 45
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 53 Asp Asn Lys Ile Thr Lys Ser Arg Arg Cys Lys Arg Ile Lys Leu Cys
 54 50 55 60
 56 aaa aag gat tta ata gat att ggt gca ata aag aaa cca att aat gla 240
 57 Lys Lys Asp Leu Ile Asp Ile Gly Ala Ile Lys Lys Pro Ile Asn Val
 58 65 70 75 80
 60 gca att ttt gga agt act ggt agt ata ggt acg aat gct tta aat ata 288
 61 Ala Ile Phe Gly Ser Thr Gly Ser Ile Gly Thr Asn Ala Leu Asn Ile
 62 85 90 95
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RAW SEQUENCE LISTING

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73 Leu Pro Glu Tyr Leu Cys Ile His Asp Lys Ser Val Tyr Glu Glu Leu
74 130 135 140
76 aaa gaa ctg gta aaa aat ata aaa gat tat aaa cct ata ata ttg tgt 480
77 Lys Glu Leu Val Lys Asn Ile Lys Asp Tyr Lys Pro Ile Ile Leu Cys
78 145 150 155 160
80 ggt gat gaa ggg atg aaa gaa ata tgt agt agt aat agt ata gat aaa 528
81 Gly Asp Glu Gly Met Lys Glu Ile Cys Ser Ser Asn Ser Ile Asp Lys
82 165 170 175
84 ata gtt att ggt att gat tct ttt caa gga tta tat tct act atg tat 576
85 Ile Val Ile Gly Ile Asp Ser Phe Gln Gly Leu Tyr Ser Thr Met Tyr
86 180 185 190
88 gca att atg aat aat aaa ata gtt gcg tta gct aat aaa gaa tcc att 624
89 Ala Ile Met Asn Asn Lys Ile Val Ala Leu Ala Asn Lys Glu Ser Ile
90 195 200 205
92 gtc tct gct ggt ttc ttt tta aag aaa tta tta aat att cat aaa aat 672
93 Val Ser Ala Gly Phe Phe Leu Lys Lys Leu Leu Asn Ile His Lys Asn
94 210 215 220
96 gca aag ata ata cct gtt gat tca gaa cat agt gct ata ttt caa tgt 720
97 Ala Lys Ile Ile Pro Val Asp Ser Glu His Ser Ala Ile Phe Gln Cys
98 225 230 235 240
100 tta gat aat aat aag gla lta aaa aca aaa tgt tta caa gac aat ttt 768
101 Leu Asp Asn Asn Lys Val Leu Lys Thr Lys Cys Leu Gln Asp Asn Phe
102 245 250 255
104 tct aaa att aac aat ata aat aaa ata ttt tta tgt tca tct gga ggt 816
105 Ser Lys Ile Asn Asn Ile Asn Lys Ile Phe Leu Cys Ser Ser Gly Gly
106 260 265 270
108 cca ttt caa aat tta act atg gac gaa tta aaa aat gta aca tca gaa 864
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130 355 360 365
132 aca tgg cct gat aga ata aaa aca aat tta aaa cct tta gat ttg gct 1152
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141 Cys Ile Lys Leu Ala Tyr Gln Ala Gly Ile Lys Gly Asn Phe Tyr Pro
142 405 410 415
144 act gta cta aat gcg tca aat gaa ata gct aac aac tta ttt ttg aat 1296
145 Thr Val Leu Asn Ala Ser Asn Glu Ile Ala Asn Asn Leu Phe Leu Asn
146 420 425 430
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181 50 55 60
183 Lys Lys Asp Leu Ile Asp Ile Gly Ala Ile Lys Lys Pro Ile Asn Val
184 65 70 75 80
186 Ala Ile Phe Gly Ser Thr Gly Ser Ile Gly Thr Asn Ala Leu Asn Ile
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193 115 120 125
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196 130 135 140
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DATE: 04/16/2001

PATENT APPLICATION: US/09/806,080

TIME: 10:33:02

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 210 Val Ser Ala Gly Phe Phe Leu Lys Lys Leu Leu Asn Ile His Lys Asn
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 214 225 230 235 240
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 235 340 345 350
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 238 355 360 365
 240 Thr Trp Pro Asp Arg Ile Lys Thr Asn Leu Lys Pro Leu Asp Leu Ala
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 243 Gln Val Ser Thr Leu Thr Phe His Lys Pro Ser Leu Glu His Phe Pro
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 250 420 425 430
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 253 435 440 445
 255 Glu Ser Phe Asn Ser Gln Lys Val Ser Glu Asn Ser Glu Asp Leu Met
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288 tatca atg att ttt aat tat gtg ttt ttt aag aac ttt gta cca gtt gtt 170
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292 cta tac att ctg ctt ata ata tat att aac tta aat ggc atg aat aat 218
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305 Leu Phe Asp Ile Gly Asn Asp Asp Asn Arg Asn Thr Thr Tyr Gly Tyr
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338      195         200         205
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VERIFICATION SUMMARY

DATE: 04/16/2001

PATENT APPLICATION: US/09/806,080

TIME: 10:33:04

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L:9 M:270 C: Current Application Number differs, Replaced Current Application Number

L:10 M:271 C: Current Filing Date differs, Replaced Current Filing Date

0906080-050101

PCT

RAW SEQUENCE LISTING

DATE: 04/04/2001

PATENT APPLICATION: US/09/806,080

TIME: 11:20:05

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 7 <130> FILE REFERENCE: 15696
 C--> 9 <140> CURRENT APPLICATION NUMBER: US/09/806,080
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Does Not Comply
 Corrected Diskette Needed

See p. 4

ERRORED SEQUENCES

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 616 65 70 75 80
 618 Val Asn Val Lys Asn Asp Asp Ile Asn Ser Leu Leu Lys Asn Asn Tyr
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 625 115 120 125
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 628 130 135 140
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 633 Asn Asn Arg Asn Asn Lys Lys Asn Phe Asn Leu Leu Phe Ile Asn Tyr
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 636 Phe Asn Leu Lys Arg Met Lys Asn Ser Leu Leu Asn Lys Asp Asn Phe
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RAW SEQUENCE LISTING

DATE: 04/04/2001

PATENT APPLICATION: US/09/806,080

TIME: 11:20:06

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652      260                265                270
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655      275                280                285
657 Arg Ser Asn His Tyr Asp Asn Tyr Gly Gly Asp Asn Asn Asn Pro Cys
658 290                295                300
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661 305                310                315                320
663 Asn Thr Phe Ile Asn Ile Asp Glu Tyr Lys Thr Ile Tyr Gly Asp Glu
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676 385                390                395                400
678 Tyr Tyr Lys Lys Glu Asn Ile Leu Ile Met Lys Lys Ile Leu His Tyr
679      405                410                415
681 Phe Pro Leu Leu Lys Leu Ile Asn Asn Pro Ser Asp Leu Lys Lys Leu
682      420                425                430
684 Lys Lys Gln Tyr Leu Pro Leu Leu Ala His Glu Leu Lys Ile Phe Leu
685      435                440                445
687 Phe Phe Ile Val Asn Ile Thr Gly Gly His Phe Ser Ser Val Leu Ser
688      450                455                460
690 Ser Leu Glu Ile Gln Leu Leu Leu Tyr Ile Phe Asn Gln Pro Tyr
691 465                470                475                480
693 Asp Asn Val Ile Tyr Asp Ile Gly His Gln Ala Tyr Val His Lys Ile
694      485                490                495
696 Leu Thr Gly Arg Lys Leu Leu Phe Leu Ser Leu Arg Asn Lys Lys Gly
697      500                505                510
699 Ile Ser Gly Phe Leu Asn Ile Phe Glu Ser Ile Tyr Asp Lys Phe Gly
700      515                520                525
702 Ala Gly His Ser Ser Thr Ser Leu Ser Ala Ile Gln Gly Tyr Tyr Glu
703      530                535                540
705 Ala Glu Trp Gln Val Lys Asn Lys Glu Lys Tyr Gly Asn Gly Asp Ile
706 545                550                555                560
708 Glu Ile Ser Asp Asn Ala Asn Val Thr Asn Asn Glu Arg Ile Phe Gln
709      565                570                575
711 Lys Gly Ile His Asn Asp Asn Asn Ile Asn Asn Asn Ile Asn Asn Asn
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TIME: 11:20:06

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DATE: 04/04/2001

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792 Ser Lys Asn Ile Asp Val Asn Val Asp Ile Asn Asp Asp Val Asp Lys
793      1010      1015      1020
795 Tyr Ser Glu Glu Tyr Met Asp Asp Asp Asn Phe Ile Lys Ser Phe Ile
E--> 796 025      1030      1035      1040
798 Gly Lys Ser Arg Ile Ile Lys Met Asp Asn Glu Asn Asn Asn Thr Asn
799      1045      1050      1055
801 Glu His Tyr Ser Ser Arg Gly Asp Thr Gln Thr Lys Lys Lys Lys Val
802      1060      1065      1070
804 Cys Ile Phe Asn Met Gly Ser Met Leu Phe Asn Val Ile Asn Ala Ile
805      1075      1080      1085
807 Lys Glu Ile Glu Lys Glu Gln Tyr Ile Ser His Asn Tyr Ser Phe Ser
808      1090      1095      1100
810 Ile Val Asp Met Ile Phe Leu Asn Pro Leu Asp Lys Asn Met Ile Asp
E--> 811 105      1110      1115      1120
813 His Val Ile Lys Gln Asn Lys His Gln Tyr Leu Ile Thr Tyr Glu Asp
814      1125      1130      1135
816 Asn Thr Ile Gly Gly Phe Ser Thr His Phe Asn Asn Tyr Leu Ile Glu
817      1140      1145      1150
819 Asn Asn Tyr Ile Thr Lys His Asn Leu Tyr Val His Asn Ile Tyr Leu
820      1155      1160      1165
822 Ser Asn Glu Pro Ile Glu His Ala Ser Phe Lys Asp Gln Gln Glu Val
823      1170      1175      1180
825 Val Lys Met Asp Lys Cys Ser Leu Val Asn Arg Ile Lys Asn Tyr Leu
E--> 826 185      1190      1195      1200
828 Lys Asn Asn Pro Thr
829      1205

```

*Invalid amino acid numbers.
 Move numbers circled one space
 to the right as shown below.*

*Tyr
 1 0 2 5*

*Ile
 1 1 0 5*

*Val
 1 1 8 5*

VERIFICATION SUMMARY

DATE: 04/04/2001

PATENT APPLICATION: US/09/806,080

TIME: 11:20:07

Input Set : A:\S0109991.app

Output Set: N:\CRF3\04042001\I806080.raw

L:1 M:259 W: Allowed number of lines exceeded, (1) GENERAL INFORMATION:
L:9 M:270 C: Current Application Number differs, Replaced Current Application Number
L:10 M:271 C: Current Filing Date differs, Replaced Current Filing Date
L:796 M:332 E: (32) Invalid/Missing Amino Acid Numbering, SEQ ID:4
M:332, Repeated in SeqNo=4

09/806080

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:
Jomaa

Serial No.: United States National Phase
of PCT/EP99/07055

Filed: Herewith

For: GENES OF THE 1-DEOXY
D-XYLULOSE BIOSYNTHESIS
PATHWAY

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Attorney Docket No.: 12964.23

I. A. Filing Date: 22 SEP1999

Priority Date: 22 SEP 1998

Attention: DO/EO/US
Commissioner For Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Dear Sir:

Prior to the initial examination of the above-identified application, please amend the application as follows:

IN THE CLAIMS:

6. (Amended) Process for the production of transgenic viruses, eukaryotes and prokaryotes for modifying the isoprenoid content, characterized in that a DNA sequence according to claim 4 is transferred and incorporated into the genome of viruses, eukaryotic and prokaryotic cells with or without use of a vector.

7. (Amended) Transgenic systems, in particular plants and plant cells which contain one or more DNA sequences according to one of claims 1 to 3 as "foreign" or "additional" DNA, which sequences are expressed.

8. (Amended) Expression vector containing one or more DNA sequences according to one of claims 1 to 3.

11. (Amended) Protein according to claim 9, characterized in that it a) is the product of viral, prokaryotic or eukaryotic expression of exogenous DNA, b) is coded by sequences SEQ ID no. 1, 3 or 5 or is coded by DNA sequences which hybridize with DNA sequences SEQ ID no. 1, 3, 5 or fragments of these DNA sequences in the DNA region which codes for the mature protein, or c) is coded by DNA sequences which would hybridize without degeneration of the genetic code with the sequences defined in b) and which code for a polypeptide with a corresponding amino acid sequence.

12. (Amended) Protein according to one of claims 1-3, 6, 9, 10, 11, 22 and 23 characterized in that it comprises the amino acid sequences SEQ ID no. 2, 4 or 6.

18. (Amended) Use of DNA according to one of claims 1 to 3.

Please add the following Claims 19-23.

19. Use of proteins according to claim 9.

20. Use of proteins according to Claim 10.

21. Use of transgenic systems according to claim 7 for the prevention or treatment of diseases in humans and animals.

22. Process for the production of transgenic viruses, eukaryotes and prokaryotes for modifying the isoprenoid content, characterized in that a DNA sequence according to claim 5 is transferred and incorporated into the genome of viruses, eukaryotic and prokaryotic cells with or without use of a vector.

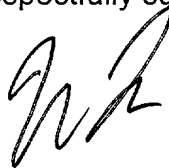
23. Protein according to claim 10, characterized in that it a) is the product of viral, prokaryotic or eukaryotic expression of exogenous DNA, b) is coded by sequences SEQ ID no. 1, 3 or 5 or is coded by DNA sequences which hybridize with DNA sequences SEQ ID no. 1, 3, 5 or fragments of these DNA sequences in the DNA region which codes for the mature protein, or c) is coded by DNA sequences which would hybridize without degeneration of the genetic code with the sequences defined in b) and which code for a polypeptide with a corresponding amino acid sequence.

REMARKS

Claims 1-23 remain in the application. Claims 6, 7, 8, 11, 12 and 18 have been amended. Claims 19-23 have been added. The filing fee has been calculated according to the above-amendments.

Should the Examiner have any questions or comments regarding the amendments, the Examiner is invited to telephone the undersigned at the number listed below.

Respectfully submitted,



Warren B. Kice
Registration No. 22,732

Dated: 3/22/01
HAYNES AND BOONE, L.L.P.
901 Main Street, Suite 3100
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Telephone: 214/651-5634
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Docket Number: 12964.23
D-880233.1

EXPRESS MAIL NO.: EL418590374US

DATE OF DEPOSIT: March 22, 2001

This paper and fee are being deposited with the U.S. Postal Service Express Mail Post Office to Addressee service under 37 CFR §1.10 on the date indicated above and is addressed to the Commissioner for Patents, Washington, D.C. 20231

SANDRA KUBIN

Name of person mailing paper and fee



Signature of person mailing paper and fee

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:
Jomaa

Serial No.: United States National Phase
of PCT/EP99/07055

Filed: Herewith

For: GENES OF THE 1-DEOXY
D-XYLULOSE BIOSYNTHESIS
PATHWAY

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Attorney Docket No.: 12964.23

I. A. Filing Date: 22 SEP1999

Priority Date: 22 SEP 1998

Attention: DO/EO/US
Commissioner For Patents
Washington, D.C. 20231

REDLINE VERSION FOR PRELIMINARY AMENDMENT

6. (Amended) Process for the production of transgenic viruses, eukaryotes and prokaryotes for modifying the isoprenoid content, [~~characterised~~] characterized in that a DNA sequence according to claim 4 [or 5] is transferred and incorporated into the genome of viruses, eukaryotic and prokaryotic cells with or without use of a vector.

7. (Amended) Transgenic systems, in particular plants and plant cells which contain one or more DNA sequences according to one of claims 1 to [5]3 as "foreign" or "additional" DNA, which sequences are expressed.

8. (Amended) Expression vector containing one or more DNA sequences according to one of claims 1 to [5] 3.

11. (Amended) Protein according to [one of] claim[s] 9 [and 10], [~~characterised~~] characterized in that it a) is the product of viral, prokaryotic or eukaryotic expression of exogenous DNA, b) is coded by sequences SEQ ID no. 1, 3 or 5 or is coded by DNA sequences which [~~hybridise~~] hybridize with DNA sequences SEQ ID no. 1, 3, 5 or fragments of these DNA sequences in the DNA region which codes for the mature protein, or c) is coded by DNA sequences which would [~~hybridise~~] hybridize without degeneration of the genetic code with the sequences defined in b) and which code for a polypeptide with a corresponding amino acid sequence.

12. (Amended) Protein according to one of [the preceding] claims 1-3, 6, 9, 10, 11, 22 and 23 [~~characterised~~] characterized in that it comprises the amino acid sequences SEQ ID no. 2, 4 or 6.

18. (Amended) Use of DNA according to one of claims 1 to [5] 3. [or of proteins according to one of claims 9 to 12 or of transgenic systems according to claim 7 for the prevention or treatment of diseases in humans and animals.]

09/806080
PTO/PCT Rec'd 01 JUN 2001

PATENT/DOCKET 12964.23

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:
Hassan Jomaa

Serial No.: 09/806,080

Filed: March 22, 2001

For: GENES OF THE 1-DEOXY D-XYLULOSE BIOSYNTHESIS PATHWAY

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I. A. Filing Date: 22 SEP1999

Priority Date: 22 SEP 1998

Attention: DO/EO/US
Box PCT
Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO COMPLY WITH REQUIREMENTS FOR SEQUENCE DISCLOSURES

Sir:

The information recorded in computer readable form (diskette sent with original filing on 22 March 2001) is identical to the written sequence listing.

We believe this response to complete the requirements under 35 U.S.C. 371.

Respectfully submitted,



Warren B. Kice
Reg. No. 22,732

Dated: 5/29/01
HAYNES AND BOONE, L.P.
901 Main Street, Suite 3100
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Docket Number: 12964.23

D-900261.1

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner For Patents, Box PCT, Washington, D.C. 20231

on

May 29, 2001
Sandra Kubin
SANDRA KUBIN

Genes of the 1-deoxy-D-xylulose biosynthesis pathway

The present invention relates to DNA sequences which, when incorporated into the genome of viruses, eukaryotes and prokaryotes, modify isoprenoid biosynthesis and to a genetic engineering process for the production of these transgenic viruses, eukaryotes and prokaryotes. The invention also relates to a process for the identification of substances having herbicidal, antimicrobial, antiparasitic, antiviral, fungicidal, bactericidal action in plants and antimicrobial, antiparasitic, antimycotic, antibacterial and antiviral action in humans and animals.

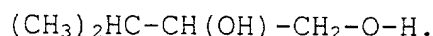
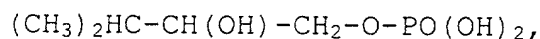
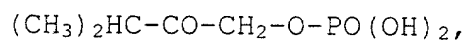
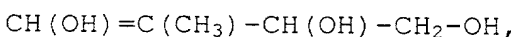
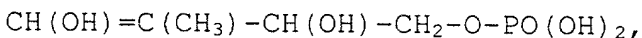
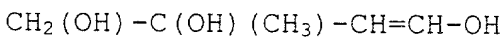
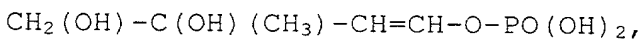
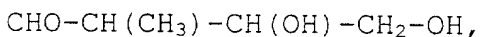
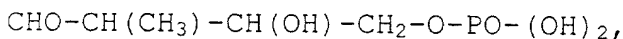
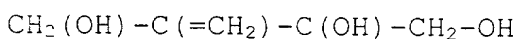
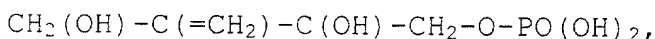
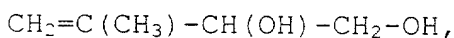
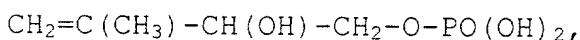
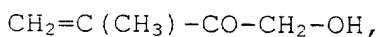
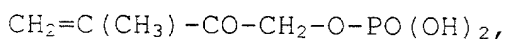
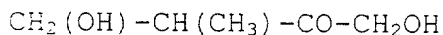
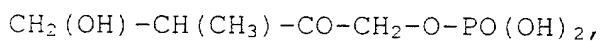
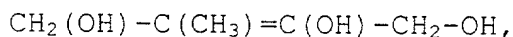
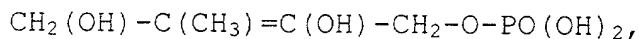
The biosynthesis pathway for the formation of isoprenoids via the classical acetate/mevalonate pathway and an alternative mevalonate-independent biosynthesis pathway, the deoxy-D-xylulose phosphate pathway is already known (Rohmer, M., Knani, M., Simonin, P., Sutter, B. and Sahm, H. (1993): *Biochem. J.* 295: 517-524).

It is, however, not known how and by which pathways it is possible to bring about a change in the isoprenoid concentration in viruses, eukaryotes and prokaryotes by means of the deoxy-D-xylulose phosphate pathway. Figure 1 shows this biosynthesis pathway.

DNA sequences are consequently provided which code for 1-deoxy-D-xylulase 5-phosphate synthase (DOXP synthase), 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DOXP reductoisomerase) or the *gcpE* protein. All three genes and enzymes are involved in isoprenoid biosynthesis.

(Translator's comment: The portion at the beginning of the next paragraph enclosed in square brackets corresponds to the beginning of the sentence which finishes on page 2, line 1 of the original).

[The gcpE protein has a kinase function and catalyses the phosphorylation of a sugar or a phosphorus sugar or a precursor of isoprenoid biosynthesis, in particular the phosphorylation of 2-C-methyl-D-erythritol, 2-C-methyl-D-erytritol phosphate, in particular 2-C-methyl-D-erythritol 4-phosphate, 2-C-methyl-D-erythrose, 2-C-methyl-D-erythrose] phosphate, in particular 2-C-methyl-D-erythrose 4-phosphate. In the precursor of isoprenoid synthesis, the gcpE protein in particular catalyses the phosphorylation of the following substances:



DOXP synthase catalyses the condensation of pyruvate and
glyceraldehyde 3-phosphate to yield 1-deoxy-D-xylulose
5-phosphate and DOXP reductoisomerase catalyses the
5 conversion of 1-deoxy-D-xylulose 5-phosphate into
2-C-methyl-D-erythritol 4-phosphate (*c.f.* Fig. 1).

The invention relates to the following DNA sequences:
DNA sequences which code for a polypeptide with the amino
10 acid sequence shown in SEQ ID no. 2 or for an analogue or
derivative of the polypeptide according to SEQ ID no. 2,
in which one or more amino acids have been deleted, added
or replaced by other amino acids, wherein the enzymatic
action of the polypeptide is retained, and which
15 sequences originate from parasites, wherein sequence
variations occurring within the framework of natural
strain variability are included,

DNA sequences which code for a polypeptide with the amino
20 acid sequence shown in SEQ ID no. 4 or for an analogue or
derivative of the polypeptide according to SEQ ID no. 4,
in which one or more amino acids have been deleted, added
or replaced by other amino acids, wherein the enzymatic
action of the polypeptide is retained, and which
25 sequences originate from parasites, wherein sequence
variations occurring within the framework of natural
strain variability are included,

and DNA sequences which code for a polypeptide with the
30 amino acid sequence shown in SEQ ID no. 6 or for an
analogue or derivative of the polypeptide according to
SEQ ID no. 6, in which one or more amino acids have been

deleted, added or replaced by other amino acids, wherein the catalytic function of the polypeptide is retained.

5 The genes and the gene products thereof (polypeptides) are shown with their primary structure and are assigned as follows:

SEQ ID no. 1: 1-deoxy-D-xylulose 5-phosphate reducto-
isomerase gene

10 SEQ ID no. 2: 1-deoxy-D-xylulose 5-phosphate reducto-
isomerase

SEQ ID no. 3: 1-deoxy-D-xylulose 5-phosphate synthase
gene

SEQ ID no. 4: 1-deoxy-D-xylulose 5-phosphate synthase

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- 4 -

SEQ ID no. 5: gcpE gene

SEQ ID no. 6: gcpE proteins.

5 The DNA sequences all originate from *Plasmodium falciparum*.

10 Apart from the DNA sequences stated in the sequence listing, suitable sequences are also those which, as a result of the degeneration of the genetic code, have another DNA sequence, but code for the same peptide or for an analogue or derivative of the polypeptide, in which one or more amino acids have been deleted, added or replaced by other amino acids.

15 The sequences according to the invention are suitable for the expression of genes in viruses, eukaryotes and prokaryotes which are responsible for isoprenoid biosynthesis in the 1-deoxy-D-xylulose pathway.

20 According to the invention, eukaryotes or eukaryotic cells include animal cells, plant cells, algae, yeasts, fungi, while prokaryotes or prokaryotic cells include bacteria, archaeobacteria and eubacteria.

25 When a DNA sequence is incorporated into a genome on which the above-stated DNA sequence is located, expression of the above-described genes in viruses, eukaryotes and prokaryotes is enabled. The viruses, eukaryotes and prokaryotes transformed according to the invention are cultivated in a manner known per se and the isoprenoid formed during such cultivation is isolated and
30 optionally purified. Not all isoprenoids need to be

- 5 -

isolated as in some case the isoprenoids are released directly into the ambient air.

The invention furthermore relates to a process for the production of transgenic viruses, eukaryotes and prokaryotes in order to modify the isoprenoid content, which process comprises the following steps.

- a) Production of a DNA sequence with the following sub-sequences
- i) promoter which is active in viruses, eukaryotes and prokaryotes and ensures the formation of an RNA in the intended target tissue or target cells,
 - ii) DNA sequence which codes for a polypeptide with the amino acid sequence shown in SEQ ID no. 2, 4 or 6 or for an analogue or derivative of the polypeptide according to SEQ ID no. 2, 4 or 6,
 - iii) 5' and 3' untranslated sequence which enables or enhances expression of the stated genes in viruses, eukaryotes and prokaryotes,
- b) transfer and incorporation of the DNA sequence into the genome of viruses, prokaryotic or eukaryotic cells with or without the use of a vector (for example plasmid, viral DNA).

The intact, whole plants may be regenerated from plant cells transformed in this manner.

The protein-coding sequences with the nucleotide sequences SEQ ID no. 1, SEQ ID no. 3 and SEQ ID no. 5 may be provided with a promoter which ensures transcription in certain organs or cells, which promoter is coupled in

- 6 -

sense orientation (3' end of the promoter to the 5' end of the coding sequence) to the sequence which codes the protein to be formed. A termination signal which determines termination of mRNA synthesis is attached to the 3' end of the coding sequence. In order to direct the protein which is to be expressed to certain subcellular compartments, such as chloroplasts, amyloplasts, mitochondria, vacuoles, cytosol or intercellular spaces, a further sequence which codes for a so-called signal sequence or a transit peptide may be inserted between the promoter and the coding sequence. In some cases, it is necessary to insert sequences which code for a signal at the COOH terminus of the protein. The sequence must be in the same reading frame as the coding sequence of the protein. A large number of cloning vectors is available in order to prepare for the introduction of the DNA sequences according to the invention into higher plants, which vectors contain a replication signal for *E. coli* and a marker which permits selection of the transformed cells. Depending upon the method by which desired genes are introduced into the plant, further DNA sequences may be required. If, for example, the Ti or Ri plasmid is used to transform the plant cells, at least one right border, but frequently the right border and left border of the Ti and Ri plasmid T-DNA must be inserted as a flanking region into the genes to be introduced. The use of T-DNA for transforming plant cells has been intensively investigated and comprehensively described in EP 120516; Hoekama in "The Binary Plant Vector System", Offset-drukkerij Kanters B.V. Alblasterdam (1985), chapter V; Fraley et al., *Crit.Rev.Plant Sci.* 4, 1-46 and An et al. (1985) *EMBO J.* 4, 277-287. Once the introduced DNA has been incorporated into the genome, it is

- 7 -

generally stable and is also retained in the descendants of the originally transformed cells. It normally contains a selection marker, which imparts to the transformed plant cells resistance to a biocide or an antibiotic, such as kanamycin, G 418, bleomycin, hygromycin or phosphinotricin and others. The particular marker used is thus intended to allow selection of transformed cells from cells lacking the inserted DNA.

Many techniques are available for introducing DNA into a plant. These techniques include transformation with the assistance of agrobacteria, for example *Agrobacterium tumefaciens*, protoplast fusion, microinjection of DNA, electroporation, as well as ballistic methods and virus infection. Whole plants may then be regenerated from the transformed plant material in a suitable medium which may contain antibiotics or biocides for selection purposes. No particular requirements are placed upon the plasmids for injection and electroporation. However, if whole plants are to be regenerated from such transformed cells, a selectable marker gene must be present. The transformed cells grow in the plants in the conventional manner (McCormick et al. (1986), *Plant Cell Reports* 5, 81-84). The plants may be cultivated normally and be crossed with plants which have the same transformed genome or other genomes. The resultant individuals have the corresponding phenotypic properties.

The present invention also provides expression vectors which contain one or more of the DNA sequences according to the invention. Such expression vectors are obtained by providing the DNA sequences according to the invention with suitable functional regulation signals. Such

- 8 -

regulation signals are DNA sequences which are responsible for expression, for example promoters, operators, enhancers, ribosomal binding sites, and are recognised by the host organism.

5

Further regulation signals, which for example control replication or recombination of the recombinant DNA in the host organism, may optionally also be a constituent part of the expression vector.

10

The host organisms transformed with the DNA sequences or expression vectors according to the invention are also provided by the present invention.

15

Suitable host cells and organisms for expressing the enzymes according to the invention are those which comprise no intrinsic enzymes with the function of DOXP synthase, DOXP reductoisomerase or the gcpE protein. This is the case for archaebacteria, animals, fungi, slime moulds and some eubacteria. The absence of such intrinsic enzyme activity substantially facilitates detection and purification of the recombinant enzymes. As a consequence, it is also for the first time possible straightforwardly to measure, in crude extracts from the host cells, the activity and in particular the inhibition of the activity of the recombinant enzymes according to the invention by various chemicals and pharmaceuticals.

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The enzymes according to the invention are advantageously then expressed in eukaryotic cells if post-translational modification and native folding of the polypeptide chain is to be achieved. Moreover, depending upon the expression system, it is ensured when expressing genomic

DNA sequences that introns are eliminated by splicing the DNA and the enzymes are produced in the polypeptide sequences characteristic to the parasites. Using recombinant DNA techniques, sequences coding for introns
5 may be eliminated from or inserted for experimental purposes into the DNA sequences to be expressed.

The protein may be isolated from the host cell or the culture supernatant of the host cell using methods known
10 to the person skilled in the art. *In vitro* reactivation of the enzymes may also be required.

In order to facilitate purification, the enzymes according to the invention or sub-sequences of the
15 enzymes may be expressed as fusion proteins with various peptide chains. Oligo-histidine sequences and sequences derived from glutathione S-transferase, thioredoxin or calmodulin-binding peptides are particularly suitable for this purpose.

20 The enzymes according to the invention or sub-sequences of the enzymes may furthermore be expressed as fusion proteins with such peptide chains known to the person skilled in the art that the recombinant enzymes are
25 transported into the extracellular medium or into certain compartments of the host cells. Both purification and investigation of the biological activity of the enzymes may consequently be facilitated.

30 When expressing the enzymes according to the invention, it may prove convenient to modify individual codons. Purposeful replacement of bases in the coding region may here also be advisable if the codons used in the

parasites differ from the codon use in the heterologous expression system, in order to ensure optimal synthesis of the protein.

5 The enzymes according to the invention may furthermore be
obtained under standardised conditions by *in vitro*
translation by methods known to the person skilled in the
art. Systems suitable for this purpose are rabbit
reticulocyte and wheat germ extracts and bacterial
10 lysates. *In vitro* transcribed mRNA may also be translated
into *Xenopus* oocytes.

Oligo- and polypeptides, the sequences of which are derived from the peptide sequence of the enzymes according to the invention, may be obtained by chemical synthesis. Given appropriate selection of the sequences, such peptides have properties which are characteristic of the enzymes according to the invention. Such peptides may be produced in large quantities and are particularly suitable for investigating the kinetics of enzyme activity, regulation of enzyme activity, the three-dimensional structure of the enzymes, inhibition of enzyme activity by various chemicals and pharmaceuticals and the binding geometry and binding affinity of various ligands.

DNA with the nucleotides from sequences SEQ ID no. 1, 3 and 5 are preferably used for the recombinant production of the enzymes according to the invention.

The invention accordingly moreover relates to a process for screening for compounds which inhibit the deoxy-D-xylulose phosphate metabolic pathway. According to this

- 11 -

process, a host organism, which contains a recombinant expression vector, wherein the vector comprises at least a portion of the oligonucleotide sequence according to SEQ ID no. 1, SEQ ID no. 3 or SEQ ID no. 5 or variants or homologues thereof, is provided, as is a compound which is suspected to have antimicrobial, antiparasitic, antibacterial, antiviral and antimycotic action in humans and animals or an antimicrobial, antiviral, bactericidal, herbicidal or fungicidal activity in plants. The host organism is then brought into contact with the compound and the activity of the compound determined.

The present invention also provides methods for determining the enzymatic activity of the gcpE protein. Said activity may be determined using known methods. Determination is performed by detecting the phosphorylation of a sugar or of a phosphorus sugar or of a precursor of isoprenoid biosynthesis, in particular the phosphorylation of 2-C-methyl-D-erythritol, 2-C-methyl-D-erythritol phosphate, in particular 2-C-methyl-D-erythritol 4-phosphate, 2-C-methyl-D-erythrose, 2-C-methyl-D-erythrose phosphate, in particular 2-C-methyl-D-erythrose 4-phosphate. The present invention also provides the use of this measurement method for identifying substances which inhibit the activity of the particular enzymes.

The enzymatic activity of DOXP synthase and DOXP reductoisomerase may be detected in a single step by determining the conversion of glyceraldehyde 3-phosphate into 2-C-methylerythritol 4-phosphate.

- 12 -

Determination of the activities of DOXP synthase and DOXP reductoisomerase proceeds analogously. Fluorimetric methods described by Querol et al. are also suitable for determining DOXP synthase activity (Querol et al.,
5 abstracts, 4th European Symposium on Plant Isoprenoids, Barcelona, 21-23 April 1999).

T07090-08090860

Claims

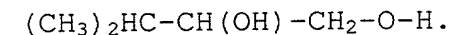
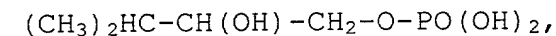
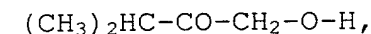
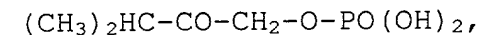
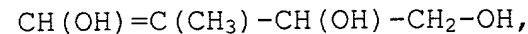
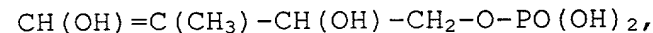
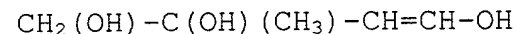
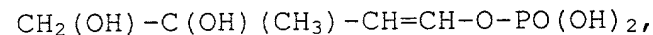
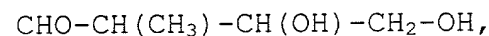
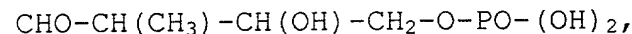
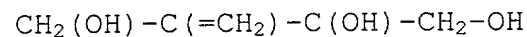
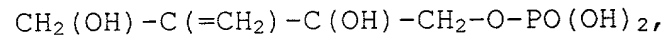
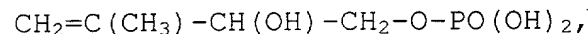
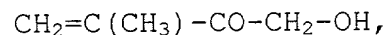
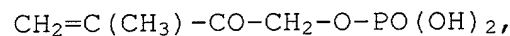
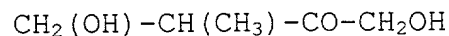
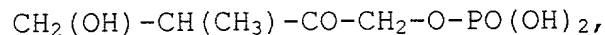
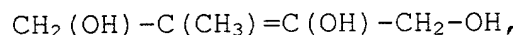
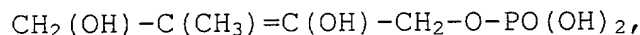
1. DNA sequences which code for a polypeptide with the amino acid sequence shown in SEQ ID no. 2 or for an analogue or derivative of the polypeptide according to SEQ ID no. 2, in which one or more amino acids have been deleted, added or replaced by other amino acids, wherein the enzymatic action of the polypeptide is retained, and which sequences originate from parasites, wherein sequence variations occurring within the framework of natural strain variability are included.
2. DNA sequences which code for a polypeptide with the amino acid sequence shown in SEQ ID no. 4 or for an analogue or derivative of the polypeptide according to SEQ ID no. 4, in which one or more amino acids have been deleted, added or replaced by other amino acids, wherein the enzymatic action of the polypeptide is retained, and which sequences originate from parasites, wherein sequence variations occurring within the framework of natural strain variability are included.
3. DNA sequences which code for a polypeptide with the amino acid sequence shown in SEQ ID no. 6 or for an analogue or derivative of the polypeptide according to SEQ ID no. 6, in which one or more amino acids have been deleted, added or replaced by other amino acids wherein the catalytic function of the polypeptide is retained.

4. DNA sequence according to one of claims 1 to 3,
characterised in that it also comprises functional
regulation signals, in particular promoters,
operators, enhancers, ribosomal binding sites.
- 5
5. DNA sequence with the following sub-sequences
- i) promoter which is active in viruses, eukaryotes
and prokaryotes and ensures the formation of an
RNA in the intended target tissue or target
cells,
- 10 ii) DNA sequences according to one of claims 1
to 3,
- iii) 3' untranslated sequence which, in viruses,
eukaryotes and prokaryotes, results in the
addition of poly(A) residues onto the 3' end of
the RNA.
- 15
6. Process for the production of transgenic viruses,
eukaryotes and prokaryotes for modifying the
isoprenoid content, characterised in that a DNA
sequence according to claim 4 or 5 is transferred
and incorporated into the genome of viruses,
eukaryotic and prokaryotic cells with or without use
of a vector.
- 20
7. Transgenic systems, in particular plants and plant
cells which contain one or more DNA sequences
according to claims 1 to 5 as "foreign" or
"additional" DNA, which sequences are expressed.
- 25
8. Expression vector containing one or more DNA
sequences according to claims 1 to 5.
- 30

9. Protein which is involved in the 1-deoxy-D-xylulose 5-phosphate metabolic pathway and a) is coded by DNA sequences SEQ ID no. 1, 3 or 5 or b) is coded by DNA sequences which hybridise with DNA sequences SEQ ID no. 1, 3, 5 or fragments of these DNA sequences in the DNA region which codes for the mature protein.
10. Protein according to claim 9, obtainable from the culture supernatants of parasites or from the disrupted parasites and purification by chromatographic and electrophoretic methods.
11. Protein according to one of claims 9 and 10, characterised in that it a) is the product of viral, prokaryotic or eukaryotic expression of exogenous DNA, b) is coded by sequences SEQ ID no. 1, 3 or 5 or is coded by DNA sequences which hybridise with DNA sequences SEQ ID no. 1, 3, 5 or fragments of these DNA sequences in the DNA region which codes for the mature protein, or c) is coded by DNA sequences which would hybridise without degeneration of the genetic code with the sequences defined in b) and which code for a polypeptide with a corresponding amino acid sequence.
12. Protein according to one of the preceding claims, characterised in that it comprises the amino acid sequences SEQ ID no. 2, 4 or 6.
13. Process for determining the enzymatic activity of the gcpE protein, characterised in that phosphorylation of a sugar or of a phosphorus sugar or of a precursor of isoprenoid biosynthesis, in

particular the phosphorylation of 2-C-methyl-D-erythritol, 2-C-methyl-D-erythritol phosphate, in particular 2-C-methyl-D-erythritol 4-phosphate, 2-C-methyl-D-erythrose, 2-C-methyl-D-erythrose phosphate, in particular 2-C-methyl-D-erythrose 4-phosphate, and of phosphate and alcohol precursors, is detected.

14. Process according to claim 13, characterised in that phosphorylation of the following phosphates or alcohols is detected:



15. Process for the combined determination of the enzymatic activity of DOXP synthase and of DOXP reductase, characterised in that the conversion of glyceraldehyde 3-phosphate into 2-C-methylerythritol 4-phosphate is detected.
16. Process for screening a compound for the treatment of infectious processes in humans and animals, wherein the process comprises:
- a) provision of a host cell which contains a recombinant expression vector, wherein the vector comprises at least a portion of the oligonucleotide sequence according to SEQ ID no. 1, SEQ ID no. 3 or SEQ ID no. 5 or variants or analogues thereof, and moreover of a compound suspected to have antimycotic, antibiotic, antiparasitic or antiviral action in humans and animals,
 - b) bringing the host cell into contact with the compound and
 - c) determining the antimicrobial, antimycotic, antibiotic, antiparasitic or antiviral action of the compound.
17. Process for screening for compounds for treating plants, wherein the process comprises:
- a) provision of a host cell which contains a recombinant expression vector, wherein the vector comprises at least a portion of the oligonucleotide sequence according to SEQ ID no. 1, SEQ ID no. 3 or SEQ ID no. 5 or variants or analogues thereof, and moreover of a compound suspected to have antimicrobial,

- antiviral, antiparasitic, bactericidal,
fungicidal or herbicidal action in plants,
- b) bringing the host cell into contact with the
compound and
- 5 c) determining the antimicrobial, antiviral,
antiparasitic, bactericidal, fungicidal or
herbicidal action of the compound.

- 10 18. Use of DNA according to one of claims 1 to 5 or of
proteins according to one of claims 9 to 12 or of
transgenic systems according to claim 7 for the
prevention or treatment of diseases in humans and
animals.

09/806080

SEQUENCE LISTING

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<140> PCT/EP99

<141> 1999-09-22

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<151> 1999-05-22

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09/806080

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 355 360 365

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 Leu Phe Asp Ile Asp Lys Tyr Asn Asp Val Glu Phe Glu Lys Ala Ile
 370 375 380

aaa gaa gaa ttt ata aat aat gga gtt tat att aat aat ata gat aat 1322
 Lys Glu Glu Phe Ile Asn Asn Gly Val Tyr Ile Asn Asn Ile Asp Asn
 385 390 395

aca tat tat aaa aaa gaa aat att tta ata atg aaa aag ata tta cat 1370
 Thr Tyr Tyr Lys Lys Glu Asn Ile Leu Ile Met Lys Lys Ile Leu His
 400 405 410 415

tat ttc cca tta tta aaa tta att aat aat cca tca gat tta aaa aag 1418
 Tyr Phe Pro Leu Leu Lys Leu Ile Asn Asn Pro Ser Asp Leu Lys Lys
 420 425 430

tta aaa aaa caa tat tta cct tta tta gca cat gaa tta aaa ata ttt 1466
 Leu Lys Lys Gln Tyr Leu Pro Leu Leu Ala His Glu Leu Lys Ile Phe
 435 440 445

098060000 0001001

| | | | | | | | | | | | | | | | | |
|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
| tta | ttt | ttt | att | gta | aat | ata | aca | gga | ggg | cat | ttt | tcc | tct | gtt | tta | 1514 |
| Leu | Phe | Phe | Ile | Val | Asn | Ile | Thr | Gly | Gly | His | Phe | Ser | Ser | Val | Leu | |
| | | 450 | | | | | 455 | | | | | 460 | | | | |
| agc | tct | tta | gaa | att | caa | tta | tta | tta | ttg | tat | att | ttt | aat | caa | cca | 1562 |
| Ser | Ser | Leu | Glu | Ile | Gln | Leu | Leu | Leu | Leu | Tyr | Ile | Phe | Asn | Gln | Pro | |
| | | 465 | | | | 470 | | | | | 475 | | | | | |
| tat | gat | aat | gtt | ata | tat | gat | ata | gga | cat | caa | gca | tat | gta | cat | aag | 1610 |
| Tyr | Asp | Asn | Val | Ile | Tyr | Asp | Ile | Gly | His | Gln | Ala | Tyr | Val | His | Lys | |
| | | | | | 485 | | | | | 490 | | | | | 495 | |
| ata | ttg | acc | gga | aga | aaa | cta | tta | ttt | cta | tca | tta | aga | aat | aaa | aaa | 1658 |
| Ile | Leu | Thr | Gly | Arg | Lys | Leu | Leu | Phe | Leu | Ser | Leu | Arg | Asn | Lys | Lys | |
| | | | | 500 | | | | | 505 | | | | | 510 | | |
| ggg | att | agt | gga | ttc | cta | aat | att | ttt | gaa | agt | att | tat | gat | aaa | ttt | 1706 |
| Gly | Ile | Ser | Gly | Phe | Leu | Asn | Ile | Phe | Glu | Ser | Ile | Tyr | Asp | Lys | Phe | |
| | | | 515 | | | | | 520 | | | | | 525 | | | |
| ggg | gct | ggg | cac | agt | tcc | act | tca | tta | agt | gct | ata | caa | gga | tat | tat | 1754 |
| Gly | Ala | Gly | His | Ser | Ser | Thr | Ser | Leu | Ser | Ala | Ile | Gln | Gly | Tyr | Tyr | |
| | | 530 | | | | | 535 | | | | | 540 | | | | |
| gaa | gcc | gag | tggt | caa | gtg | aag | aat | aaa | gaa | aaa | tat | gga | aat | gga | gat | 1802 |
| Glu | Ala | Glu | Trp | Gln | Val | Lys | Asn | Lys | Glu | Lys | Tyr | Gly | Asn | Gly | Asp | |
| | | 545 | | | | 550 | | | | | 555 | | | | | |
| ata | gaa | ata | agt | gat | aac | gca | aat | gtc | acg | aat | aat | gaa | agg | ata | ttt | 1850 |
| Ile | Glu | Ile | Ser | Asp | Asn | Ala | Asn | Val | Thr | Asn | Asn | Glu | Arg | Ile | Phe | |
| | | | | | 565 | | | | | 570 | | | | | 575 | |
| caa | aaa | gga | ata | cac | aat | gat | aat | aat | att | aac | aat | aat | att | aat | aat | 1898 |
| Gln | Lys | Gly | Ile | His | Asn | Asp | Asn | Asn | Ile | Asn | Asn | Asn | Ile | Asn | Asn | |
| | | | | 580 | | | | | 585 | | | | | 590 | | |
| aat | aat | tat | atc | aat | cct | tca | gat | gtg | gta | gga | aga | gaa | aat | acg | aat | 1946 |
| Asn | Asn | Tyr | Ile | Asn | Pro | Ser | Asp | Val | Val | Gly | Arg | Glu | Asn | Thr | Asn | |
| | | | 595 | | | | | 600 | | | | | 605 | | | |
| gta | cca | aat | gta | cga | aat | gat | aac | cat | aac | gtg | gat | aaa | gta | cac | att | 1994 |
| Val | Pro | Asn | Val | Arg | Asn | Asp | Asn | His | Asn | Val | Asp | Lys | Val | His | Ile | |
| | | 610 | | | | | 615 | | | | | 620 | | | | |
| gct | att | ata | gga | gat | ggg | ggg | tta | aca | ggg | gga | atg | gca | tta | gaa | gcg | 2042 |
| Ala | Ile | Ile | Gly | Asp | Gly | Gly | Leu | Thr | Gly | Gly | Met | Ala | Leu | Glu | Ala | |
| | | 625 | | | | 630 | | | | | 635 | | | | | |
| tta | aat | tat | att | tca | ttc | ttg | aat | tct | aaa | att | tta | att | att | tat | aat | 2090 |
| Leu | Asn | Tyr | Ile | Ser | Phe | Leu | Asn | Ser | Lys | Ile | Leu | Ile | Ile | Tyr | Asn | |
| | | | | | 645 | | | | | 650 | | | | | 655 | |
| gat | aac | gga | caa | gtt | tct | tta | cca | aca | aat | gcc | gta | agt | ata | tca | ggg | |

| | | | | | | | | | | | | | | | | |
|------|-----|------|------|------|-----|------|------|------|------|-----|------|------|------|-----|------|------|
| aaa | ata | caa | tta | tgt | ata | tat | tcg | acc | ttt | tta | caa | aga | gca | tat | gat | 2858 |
| Lys | Ile | Gln | Leu | Cys | Ile | Tyr | Ser | Thr | Phe | Leu | Gln | Arg | Ala | Tyr | Asp | |
| | | | 900 | | | | | | 905 | | | | | 910 | | |
| caa | att | ata | cat | gat | ctt | aat | tta | caa | aat | ata | cct | tta | aag | gtt | ata | 2906 |
| Gln | Ile | Ile | His | Asp | Leu | Asn | Leu | Gln | Asn | Ile | Pro | Leu | Lys | Val | Ile | |
| | | | 915 | | | | | 920 | | | | | 925 | | | |
| att | gga | aga | agt | gga | tta | gta | gga | gag | gat | ggg | gca | aca | cat | caa | ggc | 2954 |
| Ile | Gly | Arg | Ser | Gly | Leu | Val | Gly | Glu | Asp | Gly | Ala | Thr | His | Gln | Gly | |
| | | 930 | | | | | 935 | | | | | 940 | | | | |
| ata | tat | gat | tta | tct | tat | ctt | ggg | aca | ctt | aac | aat | gca | tat | ata | ata | 3002 |
| Ile | Tyr | Asp | Leu | Ser | Tyr | Leu | Gly | Thr | Leu | Asn | Asn | Ala | Tyr | Ile | Ile | |
| | | 945 | | | | 950 | | | | | 955 | | | | | |
| tct | cca | agt | aat | caa | gtt | gat | ttg | aaa | aga | gct | ctt | agg | ttt | gct | tat | 3050 |
| Ser | Pro | Ser | Asn | Gln | Val | Asp | Leu | Lys | Arg | Ala | Leu | Arg | Phe | Ala | Tyr | |
| 960 | | | | 965 | | | | | | 970 | | | | | 975 | |
| tta | gat | aag | gac | cat | tct | gtg | tat | ata | cgt | ata | ccc | aga | atg | aac | ata | 3098 |
| Leu | Asp | Lys | Asp | His | Ser | Val | Tyr | Ile | Arg | Ile | Pro | Arg | Met | Asn | Ile | |
| | | | | 980 | | | | | 985 | | | | | 990 | | |
| tta | agt | gat | aag | tac | atg | aaa | gga | tat | ttg | aac | att | cat | atg | aaa | aat | 3146 |
| Leu | Ser | Asp | Lys | Tyr | Met | Lys | Gly | Tyr | Leu | Asn | Ile | His | Met | Lys | Asn | |
| | | | 995 | | | | 1000 | | | | | 1005 | | | | |
| gag | agc | aaa | aat | atc | gat | gta | aac | gtg | gat | ata | aac | gat | gat | gta | gat | 3194 |
| Glu | Ser | Lys | Asn | Ile | Asp | Val | Asn | Val | Asp | Ile | Asn | Asp | Asp | Val | Asp | |
| | | 1010 | | | | 1015 | | | | | | 1020 | | | | |
| aaa | tat | agt | gaa | gaa | tat | atg | gac | gat | gat | aat | ttt | ata | aaa | tcg | ttt | 3242 |
| Lys | Tyr | Ser | Glu | Glu | Tyr | Met | Asp | Asp | Asp | Asn | Phe | Ile | Lys | Ser | Phe | |
| | | 1025 | | | | 1030 | | | | | 1035 | | | | | |
| att | gga | aaa | tct | aga | att | att | aaa | atg | gat | aat | gaa | aat | aat | aat | aca | 3290 |
| Ile | Gly | Lys | Ser | Arg | Ile | Ile | Lys | Met | Asp | Asn | Glu | Asn | Asn | Asn | Thr | |
| 1040 | | | | 1045 | | | | | 1050 | | | | | | 1055 | |
| aat | gaa | cat | tat | tca | agc | aga | gga | gat | aca | cag | aca | aaa | aaa | aaa | aaa | 3338 |
| Asn | Glu | His | Tyr | Ser | Ser | Arg | Gly | Asp | Thr | Gln | Thr | Lys | Lys | Lys | Lys | |
| | | | | 1060 | | | | 1065 | | | | | 1070 | | | |
| gtt | tgt | atc | ttt | aac | atg | ggc | agt | atg | ctt | ttt | aat | gta | att | aat | gct | 3386 |
| Val | Cys | Ile | Phe | Asn | Met | Gly | Ser | Met | Leu | Phe | Asn | Val | Ile | Asn | Ala | |
| | | | 1075 | | | | 1080 | | | | | 1085 | | | | |
| tat | aaa | gaa | att | gaa | aaa | gaa | caa | tat | att | tca | cat | aat | tat | tct | ttt | 3434 |
| Ile | Lys | Glu | Ile | Glu | Lys | Glu | Gln | Tyr | Ile | Ser | His | Asn | Tyr | Ser | Phe | |
| | | 1090 | | | | 1095 | | | | | | 1100 | | | | |

[illegible]

Ser Thr Asn Lys Ile Ser Gly Ser Ile Ser Asn Ile Cys Ser Arg Asn
115 120 125

- 12 -

Gln Lys Glu Asn Glu Gln Lys Arg Asn Lys Gln Arg Cys Leu Thr Gln
 130 135 140
 Cys His Thr Tyr Asn Met Ser His Glu Gln Asp Lys Leu Ala Asn Asp
 145 150 155 160
 Asn Asn Arg Asn Asn Lys Lys Asn Phe Asn Leu Leu Phe Ile Asn Tyr
 165 170 175
 Phe Asn Leu Lys Arg Met Lys Asn Ser Leu Leu Asn Lys Asp Asn Phe
 180 185 190
 Phe Tyr Cys Lys Glu Lys Lys Leu Ser Phe Leu His Lys Ala Tyr Lys
 195 200 205
 Lys Lys Asn Cys Thr Phe Gln Asn Tyr Ser Leu Lys Arg Lys Ser Asn
 210 215 220
 Arg Asp Ser His Lys Leu Phe Ser Gly Glu Phe Asp Asp Tyr Thr Asn
 225 230 235 240
 Asn Asn Ala Leu Tyr Glu Ser Glu Lys Lys Glu Tyr Ile Thr Leu Asn
 245 250 255
 Asn Asn Asn Lys Asn Asn Asn Asn Lys Asn Asn Asp Asn Lys Asn Asn
 260 265 270
 Asp Asn Asn Asp Tyr Asn Asn Asn Asn Ser Cys Asn Asn Leu Gly Glu
 275 280 285
 Arg Ser Asn His Tyr Asp Asn Tyr Gly Gly Asp Asn Asn Asn Pro Cys
 290 295 300
 Asn Asn Asn Asn Asp Lys Tyr Asp Ile Gly Lys Tyr Phe Lys Gln Ile
 305 310 315 320
 Asn Thr Phe Ile Asn Ile Asp Glu Tyr Lys Thr Ile Tyr Gly Asp Glu
 325 330 335
 Ile Tyr Lys Glu Ile Tyr Glu Leu Tyr Val Glu Arg Asn Ile Pro Glu
 340 345 350
 Tyr Tyr Glu Arg Lys Tyr Phe Ser Glu Asp Ile Lys Lys Ser Val Leu
 355 360 365
 Phe Asp Ile Asp Lys Tyr Asn Asp Val Glu Phe Glu Lys Ala Ile Lys
 370 375 380
 Glu Glu Phe Ile Asn Asn Gly Val Tyr Ile Asn Asn Ile Asp Asn Thr
 385 390 395 400
 Tyr Tyr Lys Lys Glu Asn Ile Leu Ile Met Lys Lys Ile Leu His Tyr
 405 410 415
 Phe Pro Leu Leu Lys Leu Ile Asn Asn Pro Ser Asp Leu Lys Lys Leu
 420 425 430

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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Lys | Gln | Tyr | Leu | Pro | Leu | Leu | Ala | His | Glu | Leu | Lys | Ile | Phe | Leu |
| | | 435 | | | | | 440 | | | | | 445 | | | |
| Phe | Phe | Ile | Val | Asn | Ile | Thr | Gly | Gly | His | Phe | Ser | Ser | Val | Leu | Ser |
| | 450 | | | | | 455 | | | | | 460 | | | | |
| Ser | Leu | Glu | Ile | Gln | Leu | Leu | Leu | Leu | Tyr | Ile | Phe | Asn | Gln | Pro | Tyr |
| 465 | | | | | 470 | | | | | 475 | | | | | 480 |
| Asp | Asn | Val | Ile | Tyr | Asp | Ile | Gly | His | Gln | Ala | Tyr | Val | His | Lys | Ile |
| | | | | 485 | | | | | 490 | | | | | 495 | |
| Leu | Thr | Gly | Arg | Lys | Leu | Leu | Phe | Leu | Ser | Leu | Arg | Asn | Lys | Lys | Gly |
| | | | 500 | | | | | 505 | | | | | 510 | | |
| Ile | Ser | Gly | Phe | Leu | Asn | Ile | Phe | Glu | Ser | Ile | Tyr | Asp | Lys | Phe | Gly |
| | | 515 | | | | | 520 | | | | | 525 | | | |
| Ala | Gly | His | Ser | Ser | Thr | Ser | Leu | Ser | Ala | Ile | Gln | Gly | Tyr | Tyr | Glu |
| | 530 | | | | | 535 | | | | | 540 | | | | |
| Ala | Glu | Trp | Gln | Val | Lys | Asn | Lys | Glu | Lys | Tyr | Gly | Asn | Gly | Asp | Ile |
| 545 | | | | | 550 | | | | | 555 | | | | | 560 |
| Glu | Ile | Ser | Asp | Asn | Ala | Asn | Val | Thr | Asn | Asn | Glu | Arg | Ile | Phe | Gln |
| | | | | 565 | | | | | 570 | | | | | 575 | |
| Lys | Gly | Ile | His | Asn | Asp | Asn | Asn | Ile | Asn | Asn | Asn | Ile | Asn | Asn | Asn |
| | | | 580 | | | | | 585 | | | | | 590 | | |
| Asn | Tyr | Ile | Asn | Pro | Ser | Asp | Val | Val | Gly | Arg | Glu | Asn | Thr | Asn | Val |
| | | 595 | | | | | 600 | | | | | 605 | | | |
| Pro | Asn | Val | Arg | Asn | Asp | Asn | His | Asn | Val | Asp | Lys | Val | His | Ile | Ala |
| | 610 | | | | | 615 | | | | | 620 | | | | |
| Ile | Ile | Gly | Asp | Gly | Gly | Leu | Thr | Gly | Gly | Met | Ala | Leu | Glu | Ala | Leu |
| 625 | | | | | 630 | | | | | 635 | | | | | 640 |
| Asn | Tyr | Ile | Ser | Phe | Leu | Asn | Ser | Lys | Ile | Leu | Ile | Ile | Tyr | Asn | Asp |
| | | | | 645 | | | | | 650 | | | | | 655 | |
| Asn | Gly | Gln | Val | Ser | Leu | Pro | Thr | Asn | Ala | Val | Ser | Ile | Ser | Gly | Asn |
| | | | 660 | | | | | 665 | | | | | 670 | | |
| Arg | Pro | Ile | Gly | Ser | Ile | Ser | Asp | His | Leu | His | Tyr | Phe | Val | Ser | Asn |
| | | 675 | | | | | 680 | | | | | 685 | | | |
| Ile | Glu | Ala | Asn | Ala | Gly | Asp | Asn | Lys | Leu | Ser | Lys | Asn | Ala | Lys | Glu |
| | 690 | | | | | 695 | | | | | 700 | | | | |
| Asn | Asn | Ile | Phe | Glu | Asn | Leu | Asn | Tyr | Asp | Tyr | Ile | Gly | Val | Val | Asn |
| 705 | | | | | 710 | | | | | 715 | | | | | 720 |
| Gly | Asn | Asn | Thr | Glu | Glu | Leu | Phe | Lys | Val | Leu | Asn | Asn | Ile | Lys | Glu |
| | | | | 725 | | | | | 730 | | | | | 735 | |

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| | | | | | | | | | | | | | | | |
|-----|-----|------|-----|-----|------|-----|------|-----|-----|------|-----|------|-----|-----|------|
| Asn | Lys | Leu | Lys | Arg | Ala | Thr | Val | Leu | His | Val | Arg | Thr | Lys | Lys | Ser |
| | | | 740 | | | | | | | | | | 750 | | |
| Asn | Asp | Phe | Ile | Asn | Ser | Lys | Ser | Pro | Ile | Ser | Ile | Leu | His | Ser | Ile |
| | | 755 | | | | | 760 | | | | | 765 | | | |
| Lys | Lys | Asn | Glu | Ile | Phe | Pro | Phe | Asp | Thr | Thr | Ile | Leu | Asn | Gly | Asn |
| | | 770 | | | | 775 | | | | | 780 | | | | |
| Ile | His | Lys | Glu | Asn | Lys | Ile | Glu | Glu | Glu | Lys | Asn | Val | Ser | Ser | Ser |
| 785 | | | | | 790 | | | | | 795 | | | | | 800 |
| Thr | Lys | Tyr | Asp | Val | Asn | Asn | Lys | Asn | Asn | Lys | Asn | Asn | Asp | Asn | Ser |
| | | | | 805 | | | | | 810 | | | | | 815 | |
| Glu | Ile | Ile | Lys | Tyr | Glu | Asp | Met | Phe | Ser | Lys | Glu | Thr | Phe | Thr | Asp |
| | | | 820 | | | | | 825 | | | | | 830 | | |
| Ile | Tyr | Thr | Asn | Glu | Met | Leu | Lys | Tyr | Leu | Lys | Lys | Asp | Arg | Asn | Ile |
| | | | 835 | | | | 840 | | | | | 845 | | | |
| Ile | Phe | Leu | Ser | Pro | Ala | Met | Leu | Gly | Gly | Ser | Gly | Leu | Val | Lys | Ile |
| | 850 | | | | | 855 | | | | | 860 | | | | |
| Ser | Glu | Arg | Tyr | Pro | Asn | Asn | Val | Tyr | Asp | Val | Gly | Ile | Ala | Glu | Gln |
| 865 | | | | | 870 | | | | | 875 | | | | | 880 |
| His | Ser | Val | Thr | Phe | Ala | Ala | Ala | Met | Ala | Met | Asn | Lys | Lys | Leu | Lys |
| | | | | 885 | | | | | 890 | | | | | 895 | |
| Ile | Gln | Leu | Cys | Ile | Tyr | Ser | Thr | Phe | Leu | Gln | Arg | Ala | Tyr | Asp | Gln |
| | | | 900 | | | | | 905 | | | | | 910 | | |
| Ile | Ile | His | Asp | Leu | Asn | Leu | Gln | Asn | Ile | Pro | Leu | Lys | Val | Ile | Ile |
| | | 915 | | | | | 920 | | | | | 925 | | | |
| Gly | Arg | Ser | Gly | Leu | Val | Gly | Glu | Asp | Gly | Ala | Thr | His | Gln | Gly | Ile |
| | 930 | | | | | 935 | | | | | 940 | | | | |
| Tyr | Asp | Leu | Ser | Tyr | Leu | Gly | Thr | Leu | Asn | Asn | Ala | Tyr | Ile | Ile | Ser |
| 945 | | | | | 950 | | | | | 955 | | | | | 960 |
| Pro | Ser | Asn | Gln | Val | Asp | Leu | Lys | Arg | Ala | Leu | Arg | Phe | Ala | Tyr | Leu |
| | | | | 965 | | | | | 970 | | | | | 975 | |
| Asp | Lys | Asp | His | Ser | Val | Tyr | Ile | Arg | Ile | Pro | Arg | Met | Asn | Ile | Leu |
| | | | 980 | | | | | 985 | | | | | 990 | | |
| Ser | Asp | Lys | Tyr | Met | Lys | Gly | Tyr | Leu | Asn | Ile | His | Met | Lys | Asn | Glu |
| | | 995 | | | | | 1000 | | | | | 1005 | | | |
| Ser | Lys | Asn | Ile | Asp | Val | Asn | Val | Asp | Ile | Asn | Asp | Asp | Val | Asp | Lys |
| | | 1010 | | | | | 1015 | | | | | 1020 | | | |
| Tyr | Ser | Glu | Glu | Tyr | Met | Asp | Asp | Asp | Asn | Phe | Ile | Lys | Ser | Phe | Ile |
| 025 | | | | | 1030 | | | | | 1035 | | | | | 1040 |

| | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| tta | ctg | ttt | tat | tct | cat | gta | aaa | att | aaa | aaa | tta | ttt | att | aaa | att | 279 |
| Leu | Leu | Phe | Tyr | Ser | His | Val | Lys | Ile | Lys | Lys | Leu | Phe | Ile | Lys | Ile | |
| | | | 15 | | | | | 20 | | | | | 25 | | | |

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tct aat gta aac ata ttt ttt gca gaa gca aag aaa aat gga aaa aag 327
 Ser Asn Val Asn Ile Phe Phe Ala Glu Ala Lys Lys Asn Gly Lys Lys
 30 35 40

gaa ttc ttt ctt ttt tta cta aat ata aaa aaa aat agc caa cag aaa 375
 Glu Phe Phe Leu Phe Leu Leu Asn Ile Lys Lys Asn Ser Gln Gln Lys
 45 50 55

aaa act tat cat att acc aaa agg aat acc ata aat aaa agt gat ttt 423
 Lys Thr Tyr His Ile Thr Lys Arg Asn Thr Ile Asn Lys Ser Asp Phe
 60 65 70 75

tta tat tct tta cta aat gaa gaa ggg aat tct tca aaa aag gaa tat 471
 Leu Tyr Ser Leu Leu Asn Glu Glu Gly Asn Ser Ser Lys Lys Glu Tyr
 80 85 90

aaa aat tta aaa gat gaa gaa aaa tat aat atc ata caa aat ata aaa 519
 Lys Asn Leu Lys Asp Glu Glu Lys Tyr Asn Ile Ile Gln Asn Ile Lys
 95 100 105

aaa tat tgt gaa tgt act aaa aaa tat aaa agg ctc cca aca cga gaa 567
 Lys Tyr Cys Glu Cys Thr Lys Lys Tyr Lys Arg Leu Pro Thr Arg Glu
 110 115 120

gta gtt att gga aat gtt aaa att gga gga aat aat aaa ata gct att 615
 Val Val Ile Gly Asn Val Lys Ile Gly Gly Asn Asn Lys Ile Ala Ile
 125 130 135

caa act atg gct agc tgt gat aca aga aat gta gaa gaa tgt gta tat 663
 Gln Thr Met Ala Ser Cys Asp Thr Arg Asn Val Glu Glu Cys Val Tyr
 140 145 150 155

caa att aga aaa tgt aaa gat ttg ggt gct gac att gta agg ttg act 711
 Gln Ile Arg Lys Cys Lys Asp Leu Gly Ala Asp Ile Val Arg Leu Thr
 160 165 170

gtt caa gga gtt caa gaa gca caa gct agt tat cat att aaa gaa aaa 759
 Val Gln Gly Val Gln Glu Ala Gln Ala Ser Tyr His Ile Lys Glu Lys
 175 180 185

tta tta tct gaa aat gta aat atc cca tta gta gca gat att cat ttt 807
 Leu Leu Ser Glu Asn Val Asn Ile Pro Leu Val Ala Asp Ile His Phe
 190 195 200

aat cct aaa ata gct tta atg gca gct gat gtg ttt gaa aaa att cga 855
 Asn Pro Lys Ile Ala Leu Met Ala Ala Asp Val Phe Glu Lys Ile Arg
 205 210 215

gtg aat cca gga aat tat gtt gat gga aga aaa aaa tgg ata gat aaa 903
 Val Asn Pro Gly Asn Tyr Val Asp Gly Arg Lys Lys Trp Ile Asp Lys
 220 225 230 235

gtt tat aaa aat aaa gaa gaa ttt gat gaa ggg aaa tta ttt ata aaa 951
 Val Tyr Lys Thr Lys Glu Glu Phe Asp Glu Gly Lys Leu Phe Ile Lys
 240 245 250

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| His | Val | Lys | Ile | Lys | Lys | Leu | Phe | Ile | Lys | Ile | Ser | Asn | Val | Asn | Ile |
| | | | 20 | | | | | 25 | | | | | 30 | | |
| Phe | Phe | Ala | Glu | Ala | Lys | Lys | Asn | Gly | Lys | Lys | Glu | Phe | Phe | Leu | Phe |
| | | 35 | | | | | 40 | | | | | 45 | | | |
| Leu | Leu | Asn | Ile | Lys | Lys | Asn | Ser | Gln | Gln | Lys | Lys | Thr | Tyr | His | Ile |
| | 50 | | | | | 55 | | | | | 60 | | | | |
| Thr | Lys | Arg | Asn | Thr | Ile | Asn | Lys | Ser | Asp | Phe | Leu | Tyr | Ser | Leu | Leu |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |
| Asn | Glu | Glu | Gly | Asn | Ser | Ser | Lys | Lys | Glu | Tyr | Lys | Asn | Leu | Lys | Asp |
| | | | | 85 | | | | | 90 | | | | | 95 | |
| Glu | Glu | Lys | Tyr | Asn | Ile | Ile | Gln | Asn | Ile | Lys | Lys | Tyr | Cys | Glu | Cys |
| | | | 100 | | | | | 105 | | | | | 110 | | |
| Thr | Lys | Lys | Tyr | Lys | Arg | Leu | Pro | Thr | Arg | Glu | Val | Val | Ile | Gly | Asn |
| | | 115 | | | | | 120 | | | | | 125 | | | |
| Val | Lys | Ile | Gly | Gly | Asn | Asn | Lys | Ile | Ala | Ile | Gln | Thr | Met | Ala | Ser |
| | 130 | | | | | 135 | | | | | 140 | | | | |
| Cys | Asp | Thr | Arg | Asn | Val | Glu | Glu | Cys | Val | Tyr | Gln | Ile | Arg | Lys | Cys |
| 145 | | | | | 150 | | | | | 155 | | | | | 160 |
| Lys | Asp | Leu | Gly | Ala | Asp | Ile | Val | Arg | Leu | Thr | Val | Gln | Gly | Val | Gln |
| | | | | 165 | | | | | 170 | | | | | 175 | |
| Glu | Ala | Gln | Ala | Ser | Tyr | His | Ile | Lys | Glu | Lys | Leu | Leu | Ser | Glu | Asn |
| | | | 180 | | | | | 185 | | | | | 190 | | |
| Val | Asn | Ile | Pro | Leu | Val | Ala | Asp | Ile | His | Phe | Asn | Pro | Lys | Ile | Ala |
| | | 195 | | | | | 200 | | | | | 205 | | | |
| Leu | Met | Ala | Ala | Asp | Val | Phe | Glu | Lys | Ile | Arg | Val | Asn | Pro | Gly | Asn |
| | 210 | | | | | 215 | | | | | 220 | | | | |
| Tyr | Val | Asp | Gly | Arg | Lys | Lys | Trp | Ile | Asp | Lys | Val | Tyr | Lys | Thr | Lys |
| 225 | | | | | 230 | | | | | 235 | | | | | 240 |
| Glu | Glu | Phe | Asp | Glu | Gly | Lys | Leu | Phe | Ile | Lys | Glu | Lys | Phe | Val | Pro |
| | | | | 245 | | | | | 250 | | | | | 255 | |
| Leu | Ile | Glu | Lys | Cys | Lys | Arg | Leu | Asn | Arg | Ala | Ile | Arg | Ile | Gly | Thr |
| | | | 260 | | | | | 265 | | | | | 270 | | |
| Asn | His | Gly | Ser | Leu | Ser | Ser | Arg | Val | Leu | Ser | Tyr | Tyr | Gly | Asp | Thr |
| | | 275 | | | | | 280 | | | | | 285 | | | |
| Pro | Leu | Gly | Met | Val | Glu | Ser | Ala | Phe | Glu | Phe | Ser | Asp | Leu | Cys | Ile |
| | 290 | | | | | 295 | | | | | 300 | | | | |
| Glu | Asn | Asn | Phe | Tyr | Asn | Leu | Val | Phe | Ser | Met | Lys | Ala | Ser | Asn | Ala |
| 305 | | | | | 310 | | | | | 315 | | | | | 320 |
| Tyr | Val | Met | Ile | Gln | Ser | Tyr | Arg | Leu | Leu | Val | Ser | Lys | Gln | Tyr | Gln |

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| | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | | | 325 | | | | | | 330 | | | | | | 335 |
| Arg | Asn | Met | Met | Phe | Pro | Ile | His | Leu | Gly | Val | Thr | Glu | Ala | Gly | Phe | |
| | | | | 340 | | | | | 345 | | | | | 350 | | |
| Gly | Asp | Asn | Gly | Arg | Ile | Lys | Ser | Tyr | Leu | Gly | Ile | Gly | Ser | Leu | Leu | |
| | | 355 | | | | | 360 | | | | | 365 | | | | |
| Tyr | Asp | Gly | Ile | Gly | Asp | Thr | Ile | Arg | Ile | Ser | Leu | Thr | Glu | Asp | Pro | |
| | 370 | | | | | 375 | | | | | 380 | | | | | |
| Trp | Glu | Glu | Leu | Thr | Pro | Cys | Lys | Lys | Leu | Val | Glu | Asn | Leu | Lys | Lys | |
| 385 | | | | | 390 | | | | | 395 | | | | | 400 | |
| Arg | Ile | Phe | Tyr | Asn | Glu | Asn | Phe | Lys | Glu | Asp | Asn | Glu | Leu | Lys | Asn | |
| | | | | 405 | | | | | 410 | | | | | 415 | | |
| Asn | Glu | Met | Asp | Thr | Lys | Asn | Leu | Leu | Asn | Phe | Glu | Glu | Asn | Tyr | Arg | |
| | | | 420 | | | | | 425 | | | | | | 430 | | |
| Asn | Phe | Asn | Asn | Ile | Lys | Lys | Arg | Asn | Val | Glu | Lys | Asn | Asn | Asn | Val | |
| | | 435 | | | | | 440 | | | | | | 445 | | | |
| Leu | His | Glu | Glu | Cys | Thr | Ile | Gly | Asn | Val | Val | Thr | Ile | Lys | Glu | Leu | |
| | 450 | | | | | 455 | | | | | 460 | | | | | |
| Glu | Asp | Ser | Leu | Gln | Ile | Phe | Lys | Asp | Leu | Asn | Leu | Glu | Val | Asp | Ser | |
| 465 | | | | | 470 | | | | | 475 | | | | | 480 | |
| Asn | Gly | Asn | Leu | Lys | Lys | Gly | Ala | Lys | Thr | Thr | Asp | Met | Val | Ile | Ile | |
| | | | | 485 | | | | | 490 | | | | | 495 | | |
| Asn | Asp | Phe | His | Asn | Ile | Thr | Asn | Leu | Gly | Lys | Lys | Thr | Val | Asp | Lys | |
| | | | 500 | | | | | 505 | | | | | | 510 | | |
| Leu | Met | Gln | Val | Gly | Ile | Asn | Ile | Val | Val | Gln | Tyr | Glu | Pro | His | Asn | |
| | 515 | | | | | 520 | | | | | | 525 | | | | |
| Ile | Glu | Phe | Ile | Glu | Lys | Met | Glu | Pro | Asn | Asn | Asp | Asn | Asn | Asn | Asn | |
| | 530 | | | | | 535 | | | | | 540 | | | | | |
| Asn | Asn | Asn | Asn | Asn | Ile | Leu | Phe | Tyr | Val | Asp | Ile | Lys | Asn | Ile | Met | |
| 545 | | | | | 550 | | | | | 555 | | | | | 560 | |
| Asn | Ser | Ser | Glu | Lys | Asn | Ile | Lys | Leu | Ser | Asn | Ser | Lys | Gly | Tyr | Gly | |
| | | | 565 | | | | | | 570 | | | | | 575 | | |
| Leu | Ile | Leu | Asn | Gly | Lys | Glu | Asp | Ile | Gln | Thr | Ile | Lys | Lys | Ile | Lys | |
| | | | 580 | | | | | 585 | | | | | 590 | | | |
| Glu | Leu | Asn | Arg | Arg | Pro | Leu | Phe | Ile | Leu | Leu | Lys | Ser | Asp | Asn | Ile | |
| | | 595 | | | | | 600 | | | | | 605 | | | | |
| Tyr | Glu | His | Val | Leu | Ile | Thr | Arg | Arg | Ile | Asn | Glu | Leu | Leu | Gln | Ser | |
| | 610 | | | | | 615 | | | | | 620 | | | | | |
| Leu | Asn | Ile | Asn | Ile | Pro | Tyr | Ile | His | Tyr | Val | Asp | Ile | Asn | Ser | Asn | |
| 625 | | | | | 630 | | | | | 635 | | | | | 640 | |

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Asn Tyr Asp Asp Ile Leu Val Asn Ser Thr Leu Tyr Ala Gly Ser Cys
 645 650 655
 Leu Met Asp Leu Met Gly Asp Gly Leu Ile Val Asn Val Thr Asn Asp
 660 665 670
 Val Leu Thr Asn Lys Lys Lys Ile Glu Thr Lys Tyr Asp Glu Lys Glu
 675 680 685
 Glu Val Glu Glu Glu Gly Asn Asn Lys Asp Ile His Arg Leu Leu Ser
 690 695 700
 Arg Val Ala Leu Asn Ser Phe Leu Thr Leu Asn Ile Leu Gln Asp Thr
 705 710 715 720
 Arg Ile Arg Leu Phe Lys Thr Asp Tyr Ile Ala Cys Pro Ser Cys Gly
 725 730 735
 Arg Thr Leu Phe Asn Ile Gln Glu Thr Thr Lys Lys Ile Met Lys Leu
 740 745 750
 Thr Gly His Leu Lys Gly Val Lys Ile Ala Val Met Gly Cys Ile Val
 755 760 765
 Asn Gly Ile Gly Glu Met Ala Asp Ala His Phe Gly Tyr Val Gly Ser
 770 775 780
 Ala Pro Lys Lys Ile Asp Leu Tyr Tyr Gly Lys Glu Leu Val Glu Arg
 785 790 795 800
 Asn Ile Pro Glu Glu Glu Ala Cys Asp Lys Leu Ile Glu Leu Ile Lys
 805 810 815
 Lys His Asn Lys Trp Lys Asp Pro
 820

Declaration and Power of Attorney for Patent Application

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- ☐ wurde angemeldet am _____ unter der US-Anmeldenummer oder unter der Internationalen Anmeldenummer im Rahmen des Vertrags über die Zusammenarbeit auf dem Gebiet des Patentwesens (PCT) _____ und am _____ abgeändert (falls zutreffend).

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I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

the specification of which is attached hereto unless the following box is checked:

- ☐ was filed on _____ as United States Application Number or PCT International Application Number _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

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Prior Foreign Applications
(Frühere ausländische Anmeldungen)

Priority Not Claimed
Priorität nicht beansprucht

| | |
|----------|----------------|
| (Number) | Germany |
| (Nummer) | (Country) |
| | (Land) |

(Day/Month/Year Filed)
(Tag/Monat/Jahr der Anmeldung)

| | |
|----------|-----------|
| (Number) | (Country) |
| (Nummer) | (Land) |

(Day/Month/Year Filed)
(Tag/Monat/Jahr der Anmeldung)

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§ 119(e) of any United States provisional application(s) listed below.

| | |
|-------------------|---------------|
| (Application No.) | (Filing Date) |
| (Aktenzeichen) | (Anmeldetag) |

| | |
|-------------------|---------------|
| (Application No.) | (Filing Date) |
| (Aktenzeichen) | (Anmeldetag) |

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| | |
|-------------------|---------------|
| (Application No.) | (Filing Date) |
| (Aktenzeichen) | (Anmeldetag) |

| | |
|-------------------|---------------|
| (Application No.) | (Filing Date) |
| (Aktenzeichen) | (Anmeldetag) |

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Pending
(Status) (patented, pending, abandoned)
(Status) (patentiert, schwebend, aufgegeben)

(Status) (patented, pending, abandoned)
(Status) (patentiert, schwebend, aufgegeben)

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Postanschrift:

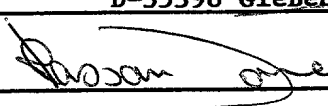
Telefonische Auskünfte: (Name und Telefonnummer)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: (list name and registration number)
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| Unterschrift des Erfinders Datum | Inventor's signature Date 28/02/07 |
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| Postanschrift | Post Office Address Breslauer Strasse 24 D-35398 Gießen, Germany |
| |  |
| Vor- und Zuname des zweiten Miterfinders (falls zutreffend) | Full name of second joint inventor, if any |
| Unterschrift des zweiten Erfinders Datum | Second Inventor's signature Date |
| Wohnsitz | Residence |
| Staatsangehörigkeit | Citizenship |
| Postanschrift | Post Office Address |
| | |

(Im Falle dritter und weiterer Miterfinder sind die entsprechenden Informationen und Unterschriften hinzuzufügen.)

(Supply similar information and signature for third and subsequent joint inventors.)